2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO COBALT IN THE UNITED STATES

Cobalt is a naturally-occurring element that has properties similar to those of iron and nickel. There is only one stable isotope of cobalt, ^{59}Co. However, there are many radioactive isotopes, two of which are commercially important, ^{60}Co and ^{57}Co. Cobalt is the 33rd most abundant element in the earth's crust. Its average concentrations in the earth's crust and in igneous rocks are 20–25 and 18 mg/kg, respectively. The United States is the world's largest consumer of cobalt. Cobalt is used in a number of essential military and industrial applications. The largest use of metallic cobalt is in superalloys that are used in gas turbine aircraft engines. Cobalt compounds are used as pigments in glass, ceramics, and paints; as catalysts in the petroleum industry; as paint driers; and as trace element additives in agriculture and medicine. ^{60}Co is produced by irradiating ^{59}Co with thermal neutrons in a nuclear reactor, and is used as a source of gamma rays for sterilizing medical equipment or consumer products, food irradiation, radiation therapy for treating cancer patients, and for manufacturing plastics. ^{57}Co decays to an excited state of ^{57}Fe, the most widely used x-ray source in Mössbauer spectroscopy.

The primary anthropogenic sources of cobalt in the environment are from the burning of fossil fuels and sewage sludge, phosphate fertilizers, mining and smelting of cobalt-containing ores, processing of cobalt-containing alloys, and industries that use or process cobalt compounds. Cobalt released to the atmosphere is deposited onto soil or water surfaces by wet and dry deposition. In soils, cobalt generally has low mobility and strong adsorption. However its mobility increases in moist, acidic soils. In water, cobalt largely partitions to sediment and suspended solids in the water column; however, the amount that is adsorbed to suspended solids is highly variable.

Exposure of the general population to cobalt occurs through inhalation of ambient air and ingestion of food and drinking water. In general, exposure from food sources is much greater than from drinking water and air. The cobalt intake in food has been estimated to be 5.0–40.0 µg/day. The general population is not significantly exposed to radioactive forms of cobalt. Cancer patients being treated with radiation therapy may be exposed to gamma rays from a ^{60}Co source; however, external exposure to gamma radiation is not unique to ^{60}Co, but is similar for all gamma-emitting radionuclides. Occupational exposure to cobalt occurs for workers in the hard metal industry (tool production, grinding, etc.) and in

industries such as coal mining, metal mining, smelting and refining, cobalt dye painters, and the cobalt chemical production industry. The concentrations of cobalt in the air of hard metal manufacturing, welding, and grinding factories may range from 1 to 300 µg/m^3, compared to normal atmospheric levels of 0.4–2.0 ng/m^3. Workers at nuclear facilities and nuclear waste storage sites may be exposed to potentially high levels of radioactive cobalt.

2.2 SUMMARY OF HEALTH EFFECTS

Overview. Cobalt is essential in the body in that it is a component of cyanocobalamin (vitamin B_{12}). Vitamin B_{12} acts as a coenzyme in many enzymatic reactions, most notably in a methyl transfer reaction that converts homocysteine to methionine and in a separate reaction that converts L-methylmalonylcoenzyme A (CoA) to succinyl-CoA. Vitamin B_{12} is also involved in some enzymes involved in hematopoiesis; deficiency can lead to pernicious anemia. It has been identified in liver, muscle, lung, lymph nodes, heart, skin, bone, hair, stomach, brain, pancreatic juice, kidneys, plasma, and urinary bladder of nonexposed subjects, with the highest cobalt concentration found in the liver. No other essential function of cobalt has been reported. The Recommended Dietary Allowance (RDA) for vitamin B_{12} for adults is 2.4 µg/day, which contains 0.1 µg of cobalt.

Cobalt has been found to produce adverse effects by the inhalation, oral, and dermal routes. Effects in humans following inhalation exposure to cobalt included lung effects (respiratory irritation, fibrosis, asthma, pneumonia, wheezing), cardiovascular effects (cardiomyopathy), liver and kidney congestion, ocular effects (congestion of the conjunctiva), and weight loss. Effects in humans observed following ingestion of cobalt, as cobalt sulfate in beer or as cobalt chloride as a treatment for anemia, included cardiomyopathy, gastrointestinal effects, visual disturbances, and thyroid effects. Cobalt dermatitis and sensitization as a result of dermal exposure to cobalt are well documented.

Exposure to sufficient levels of radiation from cobalt radionuclides may also produce adverse health effects, including respiratory pneumonitis and fibrosis, pericarditis, gastrointestinal effects, including atrophy and fibrosis of the stomach and intestines, reduced immunologic and hematologic indices, hypocellularity of bone marrow, dermal effects (including acneform reactions, hair loss, and skin degeneration), neurodegenerative and neurobehavioral effects, damage to reproductive tissues, teratogenesis, and cancer. These symptoms are the same as those experienced following exposure to other gamma-emitting isotopes.

Cobalt is essential for the growth and development of ruminants. Overexposure of other animals to cobalt resulted in effects similar to those in humans following inhalation and dermal exposure. After ingestion of cobalt, effects in animals were similar to effects in humans although some additional effects, including hypothermia, neurological effects (effects on reactivity), developmental effects (stunted fetuses), and reproductive effects (testicular degeneration and atrophy), were found in animals, but not humans. In the animal studies, the doses tested were higher than the documented levels to which humans have been exposed, or would be expected to be exposed.

Issues relevant to children are explicitly discussed in 3.6 Children's Susceptibility and 6.6 Exposures of Children.

Death. Lethal cardiomyopathy in humans was reported following repeated inhalation of airborne stable cobalt or ingestion of beer that contained cobalt. Inhalation exposure levels associated with cardiomyopathy have not been determined. In the 1960s, breweries in the United States, Canada, and Europe added cobalt salts to beer to improve foaming properties at the tap. Several deaths occurred among heavy beer drinkers who consumed beer containing 0.04–0.14 mg cobalt/kg/day (8–30 pints of beer daily). The addition of cobalt to beer has since been discontinued. Although the ingestion of cobalt was identified as a key causative factor in the beer drinkers cardiomyopathy, other etiologic factors were significant, including heavy alcohol consumption and related nutritional deficits. Repeated oral ingestion of 1 mg cobalt/kg/day to raise the hematocrit of anemic, but otherwise healthy, patients did not cause cardiac injury.

Acute exposure to high levels of radiation from a radioactive cobalt source resulted in the death of an exposed worker from acute radiation sickness. This result is not specific to cobalt radiation, and applies to all intense gamma ray emitting radionuclides.

In animals, deaths from inhalation exposure of stable cobalt were related to respiratory effects and secondary infections. Deaths in animals following oral exposure resulted from cardiomyopathy or from multiple lesions (kidney, liver, and heart lesions). Acute lethality in animals varies with the chemical form administered, with soluble compounds generally being more toxic than insoluble compounds. In rats, cobalt fluoride is more toxic than cobalt chloride by a factor of two. With the exception of tricobalt tetroxide, the LD_{50} values of the cobalt compounds for which acute oral lethality data are available (Table 3-2) all lie within the same order of magnitude when expressed in terms of the cobalt ion.

Tricobalt tetroxide (LD_{50} >3,672 mg cobalt/kg) is insoluble in water and, therefore, is relatively nontoxic. The lethal dose following exposure to cobalt radiation in animals varies with the species, portion of body exposed, dose rate, and duration of exposure.

Systemic Effects. The primary target organ systems for the effects of stable cobalt in humans are the respiratory system following inhalation exposure and the cardiac and hematopoietic systems following oral exposure. Following exposure to cobalt radiation, the most sensitive target is the developing animal, with pronounced effects also seen in the respiratory system, reproductive organs, gastrointestinal tract, blood, and nervous system.

Respiratory Effects. Effects on the respiratory system include irritation, fibrosis, asthma, pneumonia, and wheezing following inhalation exposure to stable cobalt. Individuals can develop a sensitivity to cobalt, and inhalation exposure to airborne cobalt can precipitate asthmatic attacks in sensitized individuals. Studies in animals report similar effects following inhalation exposure. Intermediate-duration inhalation studies in rats and mice reported that the larynx was the part of the respiratory tract most sensitive to the effects of cobalt, with the lungs, nose, and trachea being affected at higher exposure levels. Exposure to radiation may damage lung tissue, following a two-phase pattern. The first phase of damage usually consists of radiation pneumonitis, which occurs between 3 and 13 weeks after irradiation and is characterized by low-grade fever, mild exertional dyspnea, congestion, and unproductive cough. The second phase is characterized by radiation-induced lung fibrosis, emphysema, and pleural thickening.

Cardiovascular Effects. In humans, lethal cardiomyopathy resulted from oral and inhalation exposure to stable cobalt. Along with the severe cardiac effects, beer-cobalt cardiomyopathy was characterized by initial effects on the gastrointestinal system (vomiting, nausea, diarrhea), pulmonary rales and edema (resulting from the cardiac failure), liver injury (resulting from hepatic ischemia), and polycythemia. Beer-cobalt cardiomyopathy was similar to both alcoholic cardiomyopathy and beriberi, except that beer-cobalt cardiomyopathy had an abrupt onset, characterized by left ventricular failure, cardiogenic shock, polycythemia, and acidosis. Evidence that ingestion of ethanol was not required for development of cobalt cardiomyopathy came from studies in animals. A cardiomyopathy similar to that observed in humans occurred in guinea pigs after repeated exposure to cobalt (20 mg/kg/day) in foods, with or without ethanol consumption. Following exposure to cobalt radiation, cardiovascular effects consist mainly of pericarditis and alterations in endothelial cell permeability.

Gastrointestinal Effects. Gastrointestinal effects, including nausea, vomiting, and diarrhea, were reported in humans after ingestion of cobalt-contaminated beer and treatment with cobalt for anemia, though only a small percentage of anemic patients reported these symptoms. No effects on the gastrointestinal system were reported in animals after inhalation or oral exposure. Exposure to sufficient cobalt radiation may result in dramatic gastrointestinal effects, including vomiting, bloody stools, fibrosis, and atrophy of gastrointestinal cells.

Hematological Effects. Because stable cobalt induces polycythemia in humans following high-dose oral exposure, it has been used in the treatment of anemia. Polycythemia has not been observed in humans following inhalation exposure. Animal data show increased hematocrit and hemoglobin levels following both oral and inhalation exposure. Although increases in hematocrit in both humans and animals do not necessarily constitute an adverse effect, extreme elevation is known to increase the risk of clotting, vascular anomalies, and possible stroke. In contrast to the effects of stable cobalt, radiation from cobalt isotopes causes diminished levels of circulating erythrocytes and hemoglobin, as well as a diminished hematopoietic activity.

Musculoskeletal Effects. No studies were located demonstrating musculoskeletal effects in humans or animals following exposure to stable cobalt. The musculoskeletal system has been found to be relatively resistant to adverse effects following radiation exposure from radioactive cobalt and other radionuclides.

Hepatic Effects. No conclusive evidence that stable cobalt is a direct liver toxicant in humans has been reported following exposure to low levels; however, liver injury has been associated with cobalt-related cardiomyopathy following either inhalation or oral exposure. Although the mechanism for the liver effects is not known, it is likely that hepatic ischemia related to cardiovascular impairment is a significant causative factor. Liver injury was observed in animals orally exposed to near lethal levels of cobalt. Whether this represents a direct effect of cobalt on the liver or an indirect effect of cardiac impairment is not known. A direct effect of cobalt on the liver is plausible since the liver is the major site of accumulation of orally absorbed cobalt. Exposure to radiation from cobalt isotopes does not appear to cause significant hepatic changes unless the radiation dose is large.

Renal Effects. No conclusive evidence that stable cobalt is a kidney toxicant in humans has been reported. Congestion of the kidneys, however, has been associated with cobalt cardiomyopathy resulting from occupational exposure to cobalt. Effects on the proximal tubules of the kidneys were observed in

animals orally exposed to cobalt. Adverse effects on the kidneys of both humans and animals are a possibility because a substantial amount of cobalt absorbed into the blood is excreted in the urine. Data are not available on the effects of exposure to radiocobalt in humans, but animal studies have demonstrated a marked reduction in renal function following exposure to high levels of ^{60}Co radiation.

Endocrine Effects. Studies examining the endocrine effects of stable cobalt in humans have generally been equivocal. A decrease in iodine uptake by the thyroid resulted from acute oral exposure of humans to 1 mg cobalt/kg/day or longer-term exposure to 0.54 mg/kg/day. Exposure of animals to cobalt compounds has caused changes in histopathology of the thyroid and increased incidence of tumors of the adrenal medulla. In various species of animals, parenteral administration of cobalt resulted in cytotoxic effects on the alpha cells of the pancreas. Because this effect has never been reported in humans or animals following inhalation, oral, or dermal exposure to cobalt, the relevance of the effect to humans is not known. One study in humans exposed to cobalt radiotherapy showed that some patients developed hypothyroidism, with significant decreases in T_4 levels. Animal studies have shown no effect of cobalt radiation on levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, or testosterone.

Dermal Effects. No dermal effects have been reported following inhalation or oral exposure to stable cobalt compounds. Dermatitis is a common effect following dermal cobalt exposure in humans, and probably occurs due to an allergic reaction. Exposure to cobalt radiation may result in skin lesions, hair loss, and skin cancer.

Ocular Effects. Effects on the human eye have been observed following occupational exposure (congestion of the conjunctiva) and oral exposure (optic atrophy, impaired choroidal perfusion) to stable cobalt. Humans exposed during cobalt radiotherapy have developed vision disorders, including cataracts.

Body Weight Effects. Weight loss was found in workers occupationally exposed to stable cobalt. Similar weight loss was seen in animals. In addition, time- and dose-related hypothermia was observed in rats given cobalt orally. Available studies examining exposure to cobalt radiation have not examined alterations in body weight.

Immunological and Lymphoreticular Effects. Exposure to stable cobalt can lead to sensitization. In its most serious form, cobalt-sensitization can result in or exacerbate asthma. Dermal sensitization and related cobalt-dermatitis have also been described. The mechanism for cobalt sensitization is not completely understood. Antibodies to cobalt have been detected in individuals sensitized to cobalt, suggesting that a humoral immune response may be a component of the sensitization phenomenon. Exposure of humans to high radiation doses from cobalt isotopes results in a decrease in circulating white blood cells, particularly leucocytes and neutrophils.

Neurological Effects. No studies were located regarding neurological effects in humans following inhalation, oral, or dermal exposure to stable cobalt. Enhanced behavioral reactivity to stress, a slower rate of lever pushing, and effects on conditioned reflexes were observed in rats orally exposed to cobalt. The relevance of these findings to humans is not known. In rats, cobalt applied directly to the brain has been found to induce epilepsy and has been used extensively as a model toward a better understanding of epilepsy in humans. Isolated cases of neurological damage from cobalt radiation during radiotherapy in humans have been reported, but the results are not consistent. Animals exposed to cobalt radiation have shown changes in behavioral patterns.

Reproductive Effects. No studies were located regarding reproductive effects in humans following inhalation, oral, or dermal exposure to stable cobalt. Following both inhalation and oral exposure of animals to cobalt, adverse effects on the testes were observed (degeneration, atrophy, decreased weight). An increase in the length of the estrous cycle was also reported in female mice following inhalation exposure (NTP 1991). Because no effects on the reproductive system were found in patients who died as a result of beer-cobalt cardiomyopathy, the significance of the animal results to humans is not clear. While human data are limited, numerous animal studies have shown profound effects of cobalt radiation on the reproductive tissues of both sexes, including reduced sperm count, decreased testicular weight, decreased reproductive performance, diminished implantation, and decreased numbers of offspring per litter.

Developmental Effects. No obvious developmental effects were observed in human fetuses from mothers who were given stable cobalt orally to counteract decreases in hematocrit and hemoglobin levels that often occur during pregnancy. No studies were located regarding developmental effects in humans following inhalation or dermal exposure. Animal studies, however, reported that oral exposure to cobalt results in developmental effects including stunted fetuses, a decrease in the number of litters and average

litter weights, and an increase in the number of dead pups per litter. Toxic maternal effects were also observed in this study. The relevance of the effects found in animals to possible human effects is not known. However, exposure of male mice to cobalt (26 mg/kg/day) for 12 weeks had no effect on the offspring in the F1 generation. While human data on developmental effects following radiocobalt exposure are lacking, exposure of animals to cobalt radiation has shown dramatic effects on multiple organ systems, even at acute radiation doses as low as 10 rad (0.1 Gy) (see Section 3.2.4.6).

Cancer. Cobalt has not been shown to cause cancer in humans by the inhalation, oral, or dermal exposure routes. An occupational study reported an increased incidence of death from lung cancer (SMR=4.66) in workers exposed to cobalt, but the difference was not statistically significant. Occupational studies of hard metal exposure in humans, however, have demonstrated increased mortality from lung cancers. A lifetime inhalation exposure study of cobalt sulfate in rats and mice showed significant increases in tumor formation in both sexes of both species, with the respiratory tract being the primary site of tumor formation.

The induction of tumors (fibrosarcomas) following intramuscular injection of cobalt oxide into rats has been shown. No tumors were induced in mice after intramuscular injection of cobalt. Tumors were also induced following subcutaneous and intrathoracic injections in rats. The significance of these results to humans is not clear because these are not physiological routes of exposure and no tumors were found in humans with metal-alloy prostheses. IARC, however, has classified cobalt and cobalt compounds as group 2B, possible human carcinogens.

The carcinogenic effects of ionizing radiation are well-documented. Several human studies exist wherein cobalt radiation, given as external radiotherapy, later led to an increased incidence of cancer, generally of the skin of the treated areas.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

- An MRL of $1x10^{-4}$ mg cobalt/m^3 has been derived for chronic-duration inhalation exposure (>365 days) to cobalt.

An MRL for inhalation exposure to cobalt was derived for chronic duration only. The chronic inhalation MRL of $1x10^{-4}$ mg cobalt/m^3 was based on a NOAEL of 0.0053 mg cobalt/m^3 and LOAEL of 15.1 µg

cobalt/m^3 for decreases in forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), forced expiratory flow between 25 and 75% of the FVC (MMEF), and mean peak expiratory flow rate (PEF) in diamond polishers. The National Toxicology Program (NTP) has conducted a chronic-duration carcinogenicity study in rats and mice. Exposure of rats and mice to aerosols of cobalt (as cobalt sulfate) at concentrations ranging from 0.11 to 1.14 mg cobalt/m^3 for 2 years resulted in a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice. Squamous metaplasia of the larynx occurred in rats and mice at exposure concentrations of 0.11 mg cobalt/m^3 and above, with severity of the lesion increasing with increased exposure concentration. Hyperplastic lesions of the nasal epithelium occurred in rats at concentrations of 0.11 mg cobalt/m^3 and above, and in mice at concentrations of 0.38 mg cobalt/m^3 and above. Both sexes of rats had greatly increased incidences (>90% incidence) of alveolar lesions at all exposure levels, including inflammatory changes, fibrosis, and metaplasia. Similar changes were seen in mice at all exposure levels, though the changes in mice were less severe. The study in diamond polishers, being a well-conducted study in humans, was selected as the critical study for the derivation of a MRL because it examined a human population and defined a NOAEL, neither of which occurred in the NTP study.

An acute inhalation MRL was not derived because the threshold was not defined for human effects and animal studies reported effects that were serious and occurred at levels above those reported in the few human studies. An acute-duration study of hard metal exposure in humans was not utilized for MRL derivation because the toxicity of hard metal is not directly due to cobalt metal, but rather to an interaction between cobalt metal and tungsten carbide. An intermediate-duration MRL was not derived because available studies did not examine the dose-response relationship at low doses; the chronic inhalation MRL should be protective for intermediate exposures (see Appendix A). The chronic inhalation MRL was derived by adjusting the NOAEL of 0.0053 mg cobalt/m^3 for intermittent exposure (8 hours/24 hours x 5 days/7 days), and dividing by an uncertainty factor of 10 (for human variability). It should be noted that this MRL may not be protective for individuals already sensitive to cobalt.

Oral MRLs

- An MRL of $1x10^{-2}$ mg cobalt/kg-day has been derived for intermediate-duration oral exposure (<365 days) to cobalt.

An intermediate-duration MRL of $1x10^{-2}$ mg cobalt/kg/day was derived based on a LOAEL of 1 mg cobalt/kg-day for polycythemia as reported in a study by Davis and Fields. The authors exposed six male volunteers to 120 or 150 mg/day of cobalt chloride (~1 mg Co/kg/day) for up to 22 days. Exposure to

cobalt resulted in the development of polycythemia in all six patients, with increases in red blood cell numbers ranging from 0.5 to 1.19 million (~16–20% increase above pre-treatment levels). Polycythemic erythrocyte counts returned to normal 9–15 days after cessation of cobalt administration. An 8-week study in rats also reported increases in erythrocyte number, with a NOEL of 0.6 mg/kg-day and a LOEL of mg/kg/day.

Oral MRL values were not derived for acute or chronic exposure to cobalt. An acute MRL was not derived because the reported effects in animals were serious and occurred at levels above those reported in the few human oral studies. No chronic oral studies were available for humans or animals; therefore, a chronic oral MRL was not derived for cobalt.

Acute-, intermediate-, and chronic-duration dermal MRLs were not derived for cobalt due to the lack of appropriate methodology for the development of dermal MRLs.

MRLs for External Exposure to Cobalt Isotopes

Two MRLs have been derived for ionizing radiation and are applicable to external exposure to radioisotopes of cobalt:

- An MRL of 400 mrem (4.0 mSv) has been derived for acute-duration external exposure to ionizing radiation (14 days or less).

The acute MRL is based on results of a study in which neurological effects of radiation, measured by intelligence test scores, were evaluated in children 10–11 years of age who had been exposed at critical stages of fetal development (gestation weeks 8–15) during the atomic bombing of Hiroshima and Nagasaki. When IQ scores were regressed on radiation dose estimates, IQ diminished linearly with increasing dose, resulting in an estimated decrease in IQ score of approximately 25 points per 100 rad (or 100 rem in dose equivalent) or 0.25 points/rem (25 points/Sv). To derive the MRL of 400 mrem (4.0 mSv), ATSDR divided the dose associated with a predicted change of 0.25 IQ points/rem by an uncertainty factor of 3 (for human variability and/or the potential existence of sensitive populations). ATSDR noted that a change in IQ points of 0.25 is less than the reported difference of 0.3 IQ points between separated and unseparated identical twins.

The Nuclear Regulatory Commission (NRC) set a radiation exposure limit of 500 mrem (5 mSv) for pregnant working women over the full gestational period. For the critical gestational period of

8–15 weeks, ATSDR believes that the acute MRL of 400 mrem (4 mSv) is consistent with the NRC limit and could be applied to either acute (0–14-day) or intermediate (15–365-day) exposure periods.

- An MRL of 100 mrem/year (1.0 mSv/year) above background has been derived for chronic-duration external ionizing radiation (365 days or more).

The MRL is based on the BEIR V report that the average annual effective dose of ionizing radiation to the U.S. population is 360 mrem/year (3.6 mSv/year), a dose not expected to produce adverse non-cancerous health effects. This dose is obtained mainly by naturally-occurring radiation from external sources, medical uses of radiation, and radiation from consumer products. An uncertainty factor of 3 (for human variability) was applied to the NOAEL of 360 mrem/year to derive the MRL of 100 mrem/year.